## REMARKS

Claims 45, 46, 47, 48, 51, 52 and 57 are amended to delete non-elected subject matter based upon the discussion below. Claim 53 is canceled. No new matter is presented. Accordingly, upon entry of the Amendment, claims 45-52 and 54-57 will be all of the claims pending in the application.

### I. Restriction Requirement

The Examiner maintained the restriction requirement on the basis that although the claims are directed to methods of treatment the Examiner must perform a structure search for compounds of similar structure and use. Further, the Examiner states that the compounds defined in the claims have a heteroaryl ring wherein X is O or S and Y is optionally substituted $C_2$-$C_3$ alkylene as a common structural element, but the variables embrace a large number of compounds. The Examiner also states that the claims do not recite that $R^1$ and $R^2$ are linked to form the $C_5$-$C_7$ cycloalkyl group and therefore one would assume that the $CHR^1R^2$ group is different from the $C_5$-$C_7$ cycloalkyl.

The Examiner identified the following generic concept for examination along with the elected embodiment: compounds drawn to formula II wherein W is a $C_6$ cycloalkyl substituted by hydroxyl and optionally consisting of additional substituents; Z is imino; X is O; and Y is an optionally substituted $C_2$ alkylene. The Examiner states that the remaining subject matter of claims 45-57 is withdrawn from further consideration as constituting patentably distinct inventions.

Applicants respectfully traverse the restriction requirement for the reasons of record, which are incorporated herein. First, Applicants respectfully submit that the generic concept developed by the Examiner does not encompass the compounds elected by Applicants in the Response to Restriction Requirement filed on April 7, 2003. In the Response Applicants elected compounds drawn to formula (II) wherein:

**W** is optionally substituted $C_5$-$C_7$ cycloalkyl; $CHR^1R^2$, where $R^1$ and $R^2$ are independently selected from hydrogen, optionally substiituted $C_1$-$C_6$ alkyl, optionally substituted $C_3$-$C_7$ cycloalkyl an optionally substituted aryl;

**Z** is imino;

**X** is O; and

**Y** is optionally substituted $C_2$-$C_3$ alkylene.

Applicants further identified the following compounds identified in Table 2 on page 37 of the specification as examples of compounds falling within the scope of the elected invention:

**Rilmenidine** (W is $CHR^1R^2$, where $R^1$ and $R^2$ are independently cyclopropyl)

**BAY-A6781** (W is $CHR^1R^2$, where $R^1$ and $R^2$ are linked to form a $C_5$-$C_7$ cycloalkyl)

**(+)-S8349** (W is $CHR^1R^2$, where $R^1$ is $CF_3$ and $R^2$ is cyclopropyl)

**(-)-S8350** (W is $CHR^1R^2$, where $R^1$ is $CF_3$ and $R^2$ is cyclopropyl)

**O501** (W is $CHR^1R^2$, where $R^1$ and $R^2$ are linked to form a $C_5$-$C_7$ cycloalkyl)

**O503** (W is $CHR^1R^2$, where $R^1$ and $R^2$ are independently optionally substituted $C_3$-$C_7$ cycloalkyl)

**(S)-(+)-O504** (W is $CHR^1R^2$, where $R^1$ and $R^2$ are independently hydrogen, optionally substituted $C_1$-$C_6$ alkyl, optionally substituted $C_3$-$C_7$ cycloalkyl or optionally substituted aryl); and

**(R)-(-)O504** (W is $CHR^1R^2$, where $R^1$ and $R^2$ are independently hydrogen, optionally substituted $C_1$-$C_6$ alkyl, optionally substituted $C_3$-$C_7$ cycloalkyl or optionally substituted aryl)

However, the Examiner has defined the generic concept for examination as compounds drawn to formula (II) wherein W is $C_6$ cycloalkyl optionally substituted by hydroxyl and optionally consisting of additional substituents; Z is imino; X is O and Y is optionally substituted $C_2$ alkylene, which does not encompass the elected compounds. None of the elected compounds includes a W moiety in the form of a hydroxyl substituted $C_6$ cycloalkyl group as shown above. Further, none of the compounds specifically exemplified in the specification bears such a group. Even further, Applicants submit that original claim 1 recites an optionally substituted $C_5$-$C_7$ cycloalkyl and that by improperly choosing a $C_6$ cycloalkyl instead of a $C_5$-$C_7$ cycloalkyl, the Examiner's grouping is unduly restrictive of the claimed invention.

With respect to the Examiner's position that the claims do not recite that $R^1$ and $R^2$ are linked to form the $C_5$-$C_7$ cycloalkyl group, Applicants respectfully submit that the specification provides support for compounds where $R^1$ and $R^2$ are linked to form a $C_5$ to $C_7$ cycloalkyl group, e.g., formulae III, IV and V, which are subgroups of formula II as previously pointed out in the Response filed on April 3, 2003. Thus, Applicants have amended the claims herein to recite "W is $-CHR^1R^2$ where $R^1$ and $R^2$ are independently selected from hydrogen, optionally substituted

$C_1$-$C_6$ alkyl, optionally substituted $C_3$-$C_7$ cycloalkyl and optionally substituted aryl or $R^1$ and $R^2$ are linked to form an optionally substituted $C_5$-$C_7$ cycloalkyl.

Further, Applicants' respectfully submit that the most important compounds identified as Applicants' elected compounds are compounds of formula II, VI and VII, as represented by (+)-S8349, (-)-S8350 O503, (S)-(+)-O504 and (R)-(-)O504 in Table 2 on page 37 of the specification in which W is $CHR^1R^2$. Thus, Applicants respectfully request reconsideration of the generic concept of the elected compounds to include Applicants' elected compounds wherein W is at least $CHR^1R^2$, where $R^1$ and $R^2$ are as defined or where $R^1$ and $R^2$ are linked to form an optionally substituted $C_5$-$C_7$ cycloalkyl in the presently amended claims.

## II. Response to Claim Objections

Claims 45-57 are further objected to for containing non-elected subject matter and the Examiner suggests that Applicants limit the claims to the generic concept identified in the Office Action.

Applicants respectfully submit that the claims are amended herein to delete the non-elected subject matter in view of the traversal of the restriction requirement and definition of the generic concept identified by the Examiner set forth above. Applicants respectfully request expansion of the generic concept to include the elected compounds as defined in the presently amended claims and withdrawal of the objection to the claims.

## III. Response to Claim Rejections under 35 U.S.C. § 112, 1st Paragraph

Claims 45-57 are rejected under 35 U.S.C. § 112, 1st paragraph, as allegedly containing subject matter that is not enabled by the present specification for the reasons of record. In response to the arguments previously presented, the Examiner has indicated that the prior art does not indicate which diseases the instant compounds are useful in treating.

Applicants respectfully traverse the rejection. Applicants refer the Examiner to the following prior art references that support the treatments recited in the present claims. Copies of the references will be submitted as a supplement to this Amendment.

**W as defined in Formula II, Z=NH, Y=$CH_2CH_3$, and X=O**

1. **U.S. Pat. No. 3,598,833 (Hiltmann et al, 1971).** This patent describes aminooxazolines where W is an optionally substituted cycloalkyl. It states that it is known in the art that 2-aminooxazolines have local anesthetic properties, sedative properties and vasoconstrictory effects and have been known for use in deswelling the mucous membrane. They are also said to exhibit a strong blood pressure depressant effect and an inhibitory effect on the secretion of gastric acid.

2. **U.S. Pat. N o. 3,988,464 (Malen et al, 1976).** This patent describes aminooxazolines, where W is $CHR^1R^2$ where $R^1$ and $R^2$ are hydrogen or alkyl or cyclopropyl and $R^3$ is substituted cyclopropyl. The following pharmacological properties are disclosed: cardiovascular actions, CNS depression leading to hypnosis, analgesia and/or antipsychotic effects and a principal use as an antihypertensive.

3. **U.S. Pat. No. 4,102,890 (Malen et al, 1978).** This patent describes 2-aminooxazolines, where W is $CHR^1R^2R^3$ and $R^1$, $R^2$ and $R^3$ are hydrogen, lower alkyl or cyclopropyl. The compounds are cardiovascular agents, which depress the central nervous system with effects including hypnosis, analgesia and neuromodulation. They are also antihypertensive.

4. **DE 2,951,247 (Malen et al, 1979).** This describes aminooxazolines, where W is $CHR(CF_2)nCF_3$ and R is lower alkyl or cycloalkyl. The compounds are described as being hypotensive with weak central nervous system depressant action. They are said to be suitable as antihypertensives without sedation, drowsiness or analgesia.

5. **U.S. 4,267,345 (Malen, et al, 1981).** This patent describes aminooxazolines, where W is $CHR^1R^2R^3$ , wherein $R^1$ is $(CF_2)nCF_3$, $R^2$ is aryl 2-furyl, 2-thienyl an $R^3$ is hydrogen, methyl, ethyl or cyclopropyl. They are described as useful for treatment of hypertension.

6. **U.S. Pat. No. 4,378,366 (Malen et al, 1983).** This patent describes aminooxazolines, where W is $CHR^1R^2$ and $R^1$ is $(CF_2)nCF_3$. They are described as having antihypertensive pharmacological activity with a low degree of sedative activity.

7. **U.S. Pat. No. 5,034,406 (Gluchowski, 1991).** This patent describes aminooxazolines, where W is a substituted cycloalkyl of 5-7 carbons, preferably 6. The pharmacological properties include: local anesthetic, sedative, vasoconstriction, deswelling of mucous membranes, hypotensive and suppression of gastric secretion.

The Examiner has also suggested that the testing protocol used in the specification has not been shown to be predictive of the alleged utilities, and the art pertaining to the diseases referred to in claims 45 to 57 remain highly unpredictable.

Applicants respectfully traverse this statement. Applicants have generated a body of experimental data and published data which supports the method of treatment claims. Table I attached hereto provides affinities for the $Ox(I_3)$ receptor, the significance of which is discussed in Amendment filed on October 1, 2002.

Further, Applicants have looked at a number of the compounds in accepted experimental models of neuroprotection and have documented their ability to protect cultured neuronal cells from damage when exposed to staurosporine (3), a protein kinase inhibitor (See attached Table 2). In addition, Maiese et al (1) have demonstrated that imidazoline compounds are able to reduce the damage resulting from experimental stroke, whereas SKF86466, which is selective for the alpha2 receptor, was ineffective.

It has also been shown in other studies that the occlusion of the cerebral arteries and transient occlusion of the cerebral arteries (4-Vessel Occlusion model), which causes damage to specific neurons in the hippocampus, is associated with an increase in the number of $Ox(I_3)$ receptors on surviving neurons. This specific form of vascular damage (stroke) is something in patients after cardiac bypass surgery and is associated with memory loss. They have also seen an upregulation of these receptors in neurons in the frontal cortex and hippocampus in aged rats and in human studies of Parkinson's disease in the brain areas known to be damaged by the disease (See attached Table 3). These results provide further evidence that the Ox receptor is protective

against neuronal damage and provides strong support for the use of $Ox(I_3)$ receptor compounds in the management of stroke, Parkinson's disease and memory loss. The references are listed on the attached Appendix.

It is widely recognized that compounds that act on imidazoline receptors can lower blood pressure (4-6). This is also apparent from the patent literature and the ability of the present compounds to lower blood pressure in experimental animals has been demonstrated by the present application.

In view of the above, Applicants respectfully submit that in view of the nature of the invention, state of the prior art and level of skill in the art, and the predictability in the art, the claimed invention is sufficiently enabled by the specification and the examples therein such that one of ordinary skill in the art would be able to practice the entire scope of the claimed invention without undue experimentation.

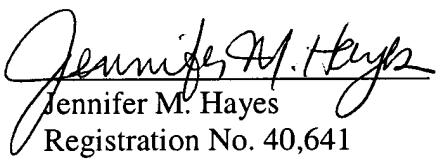
Accordingly, Applicants respectfully request withdrawal of the rejection.

## IV. Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,



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# APPENDIX

1. K. Maise, et al., "Reduction in Focal Cerebral Ischemia by Agents acting at Imidazole Receptors", J. Cereb. Blood Flow Metab. 12:53-63, 1992.

2. Craven, J. A. and Conway, E.L., Effects of Alpha2-adrenoreceptor Antagonsits and Imidazole2-receptor Ligands on Neuronal Damage In global Ischaemia in the Rat", Clin. Exp. Pharmacol. Phjysiol., 24:204-7, 1997.

3. Ryu, B.R., et al., "Attenuation of Cortical Neuronal Apoptosis by Gangliosides", J.Pharm. Exp. Ther., 280(2): 811-816, 1999.

4. Bousquet P., "Imidazoline Receptors: From Basic Concept to Recent Developments", J. Cardiovasc. Pharmacol. 26 (Suppl.2) S1-S6, 1995.

5. Bousquet, P. and Feldman , J., "Central Cardiovascular Effects of Adrenergic Drugs, Difference Between Catecholamines and Imidazolines", J.Pharmacol. Exp. Ther. 230:232-236, 1984.

6. Bousquet, P. et al., "Imidazoline Receptors and Cardiovascular Regulation: A Statement", NY ACAD Sci., 763:526-530, 1995.

## Table 1

**I3 - Oxazoline Receptor Affinities (high and low affinity sites)**

| | | | Mean f Binding affinities (nM) | |
|---|---|---|---|---|
| Compound | R1 | R2 | high affinity site * | Low affinity site |
| O503 | cyclohexyl | cyclohexyl | 117 | 2900 |
| O542 | cyclohexyl | phenyl | 28 | 4700 |
| O519 | cyclopropyl | phenyl | 13 | 675 |
| O535R | ethyl | phenyl | 9 | 1013 |
| O535S | ethyl | phenyl | 15 | 3500 |
| O535RS | ethyl | phenyl | 6 | 800 |
| O537 | hydrogen | 3,4-dimethoxyphenylmethyl | 24 | 4200 |
| O523 | hydrogen | 3,4-methylenedioxyphenoxymethyl | 2 | 517 |
| O521 | hydrogen | 3,4-methylenedioxyphenylmethyl | 13 | 1142 |
| O508 | hydrogen | 4-hydroxyphenylmethyl | 50 | 7160 |
| O511 | hydrogen | 4-methoxyphenoxymethyl | 31 | 1303 |
| O528 | hydrogen | phenylethyl | 18 | 587 |
| O544 | isobutyl | phenyl | 29 | 5150 |
| O540 | methyl | 2-hydroxyphenyl | 116 | 7667 |
| O507 | methyl | 3,methoxy,4-ethoxyphenylmethyl | | 884 |
| O520 | methyl | 3-methoxy,4-benzyloxyphenyl | 5 | 278 |
| O530 | methyl | 3-methoxy,4-hydroxyphenyl | | 1313 |
| O536S | methyl | 3-methoxyphenyl | 51 | 3075 |
| O533 | methyl | 4-(4-nitrobenzyloxy)phenyl | 128 | |
| O514 | methyl | 4-benzyloxyphenyl | 40 | |
| O514S | methyl | 4-benzyloxyphenyl | 6 | 188 |
| O514R | methyl | 4-benzyloxyphenyl | 79 | |
| O509 | methyl | 4-benzyloxyphenylmethyl | 117 | |
| N515 | methyl | 4-hydroxyphenyl | 90 | 2950 |
| O516 | methyl | 4-hydroxyphenylmethyl | 86 | 3861 |
| O504R | methyl | cyclohexyl | 32 | 907 |
| O504S | methyl | cyclohexyl | 20 | 722 |
| O505R | methyl | phenyl | 24 | 572 |
| O505S | methyl | phenyl | 36 | 2860 |
| O502 | phenyl | phenyl | 66 | 7850 |
| O543 | propyl | methyl | 25 | 6233 |
| O545 | sec butyl | phenyl | 30 | 3333 |

**Table 1:** Affinities for the Ox (I3) receptor measured in rat brain with $^{3}$H-rilmenidine. R1 and R2 are the CHR1R2 substituents referred to in formula II

* where only one affinity value is given, the binding is consistent with a single affinity site.

**Table 2**

Neuroprotective actions of Ox(I3) compounds on cultured foetal rat cells.

| Compound | Concentration of drugs found to be neuroprotective against staurosporine injury. (μM) |
|---|---|
| O528 | 0.05-1 |
| O504(s) | 0.05-1 |
| O535(R) | 0.05-1 |
| O535(RS) | 0.05-1 |

Cortical neurons from foetal rats are dissected and dispersed in culture medium, then placed in 96 well culture plates. After 24 hours in serum-containing medium, they are grown in a serum free medium and used for experiments on days 8-11.

Neuronal damage (apoptosis) can be induced by exposure of the cells to staurosporine (100 nM), a protein kinase inhibitor, for 48 hours, in the presence of the test drugs. Damage is assessed by the number of surviving cells able to oxidise MTT to a coloured formazan product. The four compounds tested are able to protect against such damage at concentrations, which are comparable with their high and low affinities for the Ox-I3 receptor.

**MTT Reduction Assay** (1)

Viable cells retain the ability to reduce MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) to formazan, which has a strong absorbance at 570nm. After injury, 0.5 mg/ml of MTT is added to control and treated wells , and these are then incubated at 37°C for 2 hours. At the end of this period the cells are lysed and formazan solubilised by the addition of an equal volume of 20% sodium dodecyl sulfate (SDS) in 50% dimethylformamide (DMF). The concentration of formazan is then estimated by UV absorbance at 570 nm.

(1) Abe, K. & Matsuki, N. (2000). Measurement of cellular 3-(4,5-dimethylthiazol-2-yl)-2,5-dipthenyltetrazolium bromide (MTT) reduction activity and lactate dehydrogenase release using MTT. *Neuroscience Research*, 38,325-29.

## Table 3

| Source | Frontal Cortex Specific Binding dpm/mm² | Neuronal Cells/mm² | Caudate Nucleus Specific Binding dpm/mm² | Neuronal Cells/mm² | Internal Globus pallidus Specific Binding dpm/mm² | Neuronal Cells/mm² | Substantia Nigra Specific Binding dpm/mm² | Neuronal Cells/mm² |
|---|---|---|---|---|---|---|---|---|
| C97 | 1084 ±302 | 495 | 7879 ±4697 | 425 ±10 | 5992 ±3274 | 60 ±1 | 4393 ±1090 | 95 ±22 |
| C101 | 1184 ±78 | 364 | 16172 ±8023 | 319 ±64 | 11192 ±4940 | 69 ±12 | 2726 ±654 | 117 ±26 |
| C91 | 1664 ±349 | 486 | 18673 ±7672 | 413 ±76 | 16997 ±5399 | 68 ±12 | 4069 ±845 | 71 ±5 |
| C96 | 1363 ±80 | 283 | 12859 ±3114 | 400 ±62 | 13337 ±4895 | 46 ±8 | 2142 ±367 | 88 ±13 |
| PD141 | 862 ±399 | 304 | 10074 ±3356 | 279 ±32 | 13216 ±3245 | 26 ±3 | 4749 ±2401 | 51 |
| PD147 | 988 ±192 | 460 | 14670 ±6681 | 278 ±67 | 13991 ±4543 | 41 ±5 | 3148 ±831 | 43 ±20 |
| PD143 | 1565 ±104 | 558 | 9999 ±4443 | 383 ±41 | 9313 ±3917 | 40 ±7 | 3409 ±158 | 71 ±18 |
| PD145 | 1440 ±177 | 326 | 18807 ±4904 | 274 ±40 | 15802 ±4408 | 28 ±7 | 2408 ±882 | 53 |
| P= | 0.31 | 0.47 | 0.44 | 0.03 | 0.33 | 0.001 | 0.45 | 0.01 |

**Table 3:** Comparison of specific receptor binding of $^{125}$I-O515 (I3-Ox receptor ligand) in brains from Parkinson's disease patients (PD prefix) and age-matched normal subjects (C prefix). Fresh frozen tissue from the regions of Frontal cortex, caudate nucleus , internal globus pallidus and substantia nigra, were cut into 20 µm sections. Adjacent sections were used for measurement of radioligand binding and measurement of cell density. Radioligand binding was quantitated by computer-aided densitometry of autoradiographic film exposed to the radiolabelled sections and expressed as dpm/mm$^2$ after calibration with known radioactive standards. Cell bodies were visualised with cresyl violet staining and counted by computer with appropriate settings for the minimum cell size and staining density. The relevant areas for study in each section were evaluated and marked by an experienced anatomical pathologist.

The neuronal cell bodies in frontal cortex, which are not normally affected by Parkinson's disease, shows no significant difference between normal controls and Parkinson's disease patients in either receptor density or cell counts. The remaining three regions are all known to be affected by Parkinson's disease and all show significantly lower cell numbers in Parkinson's disease ($P < 0.05$).In contrast, the receptor density in each of these three regions as measured by specific binding is not significantly different between Parkinson's disease patients and normal controls, despite the smaller number of neuronal cell bodies in Parkinson's disease. This result is consistent with an upregulation of the number of Ox(I3) receptors per neuron.